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Organocatalytic Cascade Reactions: Diversity-Oriented Synthesis for the Construction of Hydroisoquinoline Scaffolds

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The organocatalytic enantioselective synthesis of highly functionalized hydroisoquinolines by trienamine-mediated [4+2]-cycloaddition/nucleophilic ring-closing reaction cascade sequence of cyanoacrylamides with 2,4-dienals is presented. The corresponding cycloadducts are formed in high yields and excellent stereoselectivities. Moreover, a series of transformations demonstrate the synthetic application of the obtained hydroisoquinolines.

ŌMe

R = OMe reserpine R = H deserpidine

Introduction

Privileged molecular structures, small molecules and backbones of more complex natural architectures, have become central topics for synthetic chemists because such molecules usually exhibit important biological-activity, properties associated to its structural connectivity and shape in a three-dimensional environment.¹

As privileged structures, hydroisoquinoline scaffolds are interesting synthetic targets because they have been demonstrated to be precursors for important compounds, such as yohimboid alkaloids, of which reserpine,² deserpidine³ and yohimbines⁴ are among the most important targets (Figure 1). Particularly, reserpine which shows pharmacological activity as a nervous-system depressant and has been applied as a medicinal agent for the treatment of hypertension and mental disorders has received considerable attention.^{2b} Driven by both total and formal syntheses of reserpine, Wender, Martin and Shea independently developed methodologies for the construction of functionalized hydroisoquinoline scaffolds as key DE-ring precursors by the Diels-Alder cycloaddition/Cope rearrangement,⁵ intramolecular Diels-Alder cycloaddition of azatrienes^{2a,6}, and *N*-vinylimidates.⁷ In all these cases, the desired precursors were obtained after more than three steps and without control of absolute configuration.

Diversity-oriented synthesis (DOS) has provided efficient methodologies for the preparation of small molecules. Thus, libraries of compounds with a wide range of physical and biological properties have been prepared, including drugs, drug candidates and precursors for more complex structures.⁸ Given that the screening of small molecules has helped to identify new classes of biologically active molecules, DOS is still a challenge for an efficient generation of libraries.

In terms of diversity, organocatalysis has played an important role due to the way in which both small and complex molecules are prepared.⁹ The recent development of new organocatalytic activations involving dienamines,¹⁰ vinylogous-iminium-ions¹¹ and trienamines¹² offers new tools for DOS.

Trienamine activation is an efficient HOMO-raising strategy in organocatalysis for both simple and cascade asymmetric transfor-

Figure 1. Hydroisoquinoline scaffold occurring in natural products.

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yohimbine

organocatalysis for both simple and cascade asymmetric transformations. In the following we will apply the trienamine activation to provide an efficient methodology to access the privileged hydroisoquinoline structures through DOS. The strategy for the asymmetric synthesis of highly functionalized hydroisoquinolines is based on an organocatalytic Diels-Alder/nucleophilic ring-closing reaction cascade sequence.

As part of the strategy, we hypothesized that cyanoacrylamides might be good dienophiles¹³ to react with an activated trienamine system. The two electron-withdrawing groups attached to the double bond in the cyanoacrylamides will ensure a good reactivity toward the [4+2]-cycloaddition, while it is expected that the planarity of the molecule will provide a correct *endo-exo* selection. Finally, once the catalytic cycloaddition proceeds, a nucleophilic ring-closing reaction can take place between the nitrogen atom of the amide and the aldehyde to obtain the corresponding hydroisoquinolines in a cascade fashion (Scheme 1).

Scheme 1. Proposed reaction pathway for the organocatalytic cascade reaction providing optically active hydroisoquinoline scaffolds.



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α-yohimbine

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Results and discussion

In order to prove the feasibility of the hypothesis, we chose to study the cascade sequence between (*E*)-5-methylhexa-2,4-dienal **1a** and cyanoacrylamide **2a** as a model reaction (Table 1). In a first approach, in presence of 20 mol% of the TMS-protected prolinol catalyst **3a** and *p*-nitrobenzoic acid (*p*-NBA), the desired product **4a** was observed only with 20% of conversion after 24 h in CDCl₃ (entry 1). By changing the solvent to THF or 1,4-dioxane the conversion was enhanced to be 50 and 60% respectively (entries 2,3). Finally when the reaction was performed at 70 °C in 1,4-dioxane, full conversion, excellent diasteromeric ratio and promising enantiomeric excess of product **4a** were observed after 20 h (entry 4). However, only a moderate enantioselectivity of 70% ee of **4a** was obtained.

Table 1. Screening of the reaction conditions for the [4+2]-cycloaddition/nucleophilic ring-closing reaction of (*E*)-5-methylhexa-2,4-dienal **1a** and cyanoacrylamide **2a**.



1^a	3a	CDCl ₃	rt	24	nd	nd	20/nd
-							
2^{a}	3a	THF	rt	24	nd	nd	50/nd
3 ^{<i>a</i>}	3a	dioxane	rt	24	nd	nd	60/nd
4^b	3a	dioxane	70	20	90:10	70	>95/50
5^b	3b	dioxane	70	20	90:10	46	>95/24
6^b	3c	dioxane	70	20	90:10	84	>95/40
7^b	3d	dioxane	70	20	90:10	-63	>95/46
8^b	3e	dioxane	70	20	90:10	85	>95/43
9^b	3f	dioxane	70	20	90:10	89	>95/49
10^{b}	3g	dioxane	70	20	90:10	95	>95/53
11^{a}	3g	dioxane	70	20	90:10	95	>95/80

^{*a*}Reactions were performed with **1a** (0.2 mmol), **2a** (0.1 mmol), **3** (0.02 mmol) and *p*-NBA (0.02 mmol) in solvent (0.5 mL). ^{*b*}**1a** (0.1 mmol) and **2a** (0.2 mmol). ^cDetermined by ¹H NMR spectroscopy on the crude reaction mixture. ^{*d*}Determined by chiral ultraperformance convergence chromatography (UPC²).

In attempts to improve the enantioselectivity of the reaction, several silyl-protected prolinol catalysts **3** were tested. Interestingly, the screening showed that the enantioselectivity is very dependent on the sterics of the substituent in the silyl-protecting group. This sterics-dependence provided the Ph₃Si-protected prolinol **3g** as the best catalyst giving the hydroisoquinoline **4a** in 53% yield and 95% ee (entry 10). Finally, as it was observed at the beginning of the screening study, that small amounts of the aldehyde were degraded at 70 °C, we switched the equivalents of the reactants to be two for the aldehyde and one for the cyanoacrylamides to obtain 80% yield of **4a** (entry 11).

With the optimal conditions established, our attention was addressed towards the scope of the reaction with various dienals 1 and different cyanoacrylamides 2 (Scheme 2).

Pleasingly, a variety of substitution patterns were well-tolerated for the dienals 1 and cyanoacrylamides 2. Both electron-withdrawing and electron-donating substituents on the aromatic ring of the cyanoacrylamides 2 lead to excellent enantioselectivities (91-96% ee) and very good yields and diastereoselectivities of the hydroisoquinoline scaffolds 4b-g were obtained. Heteroaromatic substituents as well as fused aromatic rings in 2 were also compatible with the methodology and afforded the corresponding products 4h-j with



Reaction conditions: 1 (0.2 mmol), 2 (0.1 mmol), 3g (0.02 mmol) and *p*-NBA (0.02 mmol) in 0.5 mL of 1,4-dioxane. The reported yields are for the major diastereoisomer only. The dr values were determined by ¹H NMR spectroscopy on the crude mixture. The ee values (major diastereoisomer) were determined by chiral ultraperformance convergence chromatography (UPC²). ^adr was not determined.

high levels of stereocontrol (93-97% ee and 90:10 dr) and very good yields. Alkyl group in the cyanoacrylamide resulted in less reactivity and reduced stereoselectivity, probably due to a loss in the planarity of the molecule as obtained for product 4k.

Next, a variety of dienals 1, acting as trienamine precursors, were evaluated for this asymmetric Diels-Alder/nucleophilic ring-closing reaction. Delightfully, good yields and excellent stereoselectivities were also observed for the dienal precursors. It was found that alkyl and aryl substituents at γ - and δ -positions can be attached to the dienal and the corresponding products **41-q** were obtained in up to 78% yield, >95:5 dr and up to 98% ee. Interestingly, the highest diasteromeric ratios were observed when alkyl or aryl substituents at C-4 of 1 are present (**4m**,**n**). Tri- and tetracyclic products could also be prepared (**40**,**r**). Slightly lower yields were observed; however, the excellent enantioselectivities were maintained.

The absolute	configuration	of the	hydroisoqu	unoline 4b	was un-
ambiguously	established	by	X-ray	crystallog	graphy. ¹⁴

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The configurations of the remaining products **4** were assigned by analogy.

Having proved the generality of the trienamine-mediated [4+2]-cycloaddition/nucleophilic ring-closing reactions for the formation of optically active hydroisoquinoline scaffolds **4**, we moved into the synthetic potential of the various functionalities of these products. Interestingly, an epimerization of the hemiaminal stereocenter at C-3 of **4a** was observed under basic conditions (Scheme 3, eq I).¹⁵ Thus, when DMAP was added after the catalytic Diels-Alder/nucleophilic ring-closing reaction, the epimer **5** was obtained with complete inversion of the configuration, maintaining the enantioselectivity.

Furthermore, the hydroxyl group can be reduced or oxidized to the corresponding saturated product **6** or amide **7** with excellent and quantitative yields, respectively (Scheme 3, eqs II,III). Finally, a stereoselective epoxidation at the double bond was achieved, leading to the highly functionalized compound **8** with six stereocenters (Scheme 3, eq IV).

Scheme 3. Synthetic transformations of product 4a.



Conclusions

In summary, an organocatalytic cascade reaction mediated trienamine [4+2]-cycloaddition/nucleophilic ring-closing sequence has been developed. The reaction between diversely substituted cyanoacrylamides and 2,4-dienals to generate multifunctionalized hydroisoquinolines proceeded efficiently. The highly steric Ph₃Si-protecting group at the catalyst was decisive to reach high enantioselectivities. The synthetic application of the obtained cycloadducts was demonstrated. The stereochemistry at C-3 could be modulated depending on the work-up of the reaction mixture. A reduction and oxidation at the same position could also be achieved efficiently. Finally, a stereoselective epoxidation led to multifunctional hydroisoquinolines with up to six stereocenters.

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Notes and references

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- 14 See Supporting Information for details about the X-ray analysis.
- 15 It was shown by ¹H and ¹³C NMR that product **5** could be oxidized to form product **7**.

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Graphical Abstract

